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## **Human Papillomavirus (HPV): Making the case for “Immunisation for All”**

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### **Abstract**

Human Papillomavirus (HPV) contributes to the most common sexually transmitted infections, with repeated and persistent infection with particular types causing disease in both men and women. Infection with low-risk HPV types can lead to genital warts and benign lesions of the oral cavity, while high-risk types can cause various HPV-related malignancies. The incidence of head and neck cancer has been rising in the past number of decades mostly due to oropharyngeal cancer linked to HPV infection. HPV vaccination has been shown to be effective for cervical and other anogenital HPV-related cancers, and there is significant

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potential for HPV vaccination to prevent oropharyngeal cancers, given that the HPV types implicated in this disease can be protected against by the HPV vaccine. Few countries have implemented a universal HPV vaccination programme for males and females, with many countries arguing that female only vaccination programmes protect males via herd immunity, and that men-who-have-sex-with-men will be protected via targeted vaccination programmes. We argue these may be limited in their effectiveness. We propose that the most effective, practical, ethical and potentially cost effective solution is universal HPV vaccination that might lead to control of HPV-related diseases in men and women alike.

### **Human Papillomavirus (HPV) and the burden of disease**

HPV is one of the most common sexually transmitted infections; there are more than 100 types of HPV, and varying degrees of risk linked with continual infection by each type. Many infections are short-lived and clinically unimportant, but repeated infection with particular types causes a considerable burden of disease in both men and women. Infection with low-risk HPV (6/11) is implicated in the development of genital warts (Lacey et al., 2006), and many HPV-associated benign lesions of the oral cavity, while high-risk types (e.g. 16, 18) can cause HPV-related malignancies. In women, HPV prevalence peaks between 18-24 years and subsequently declines (Burchell et al., 2006). In contrast, in men, there is a consistently higher prevalence of HPV (Anic et al., 2011) due to the poorer natural immune response men mount against HPV infection compared to females (Giuliano et al., 2011). Prevalence of HPV in men varies greatly between studies, but most report a prevalence >20% (Dunne et al., 2006), with a more recent study suggesting an overall male HPV prevalence approaching 50% (Giuliano et al., 2008), with approximately 20% of men infected with one or more bivalent/quadrivalent vaccine-related types (HPV6, 11, 16, 18) (Giuliano et al., 2008).

In 2008, of the estimated 12.7 million cancers globally, 610,000 were attributable to HPV infection (Forman et al., 2012), about 5% of the total cancer burden. Cervical cancer has been unequivocally linked to persistent HPV infection, with HPV 16 and 18 implicated in 70% of cervical cancers (de Sanjose et al., 2010), and types 31, 33 and 45 linked to the majority of the remaining 30% of cases (CRUK, 2016). Approximately 95% of anal cancers are caused by HPV; 65% of vaginal cancers; 50% of vulval cancers and 35% of penile cancers (Gillison et al., 2008; Alemany et al., 2016). Anal cancer incidence has increased rapidly in recent years (Wilkinson et al., 2014), with men-who-have-sex-with-men (MSM) carrying an

unequal burden of anal cancer (15:1 compared with heterosexual men). MSM rates are similar to cervical cancer rates before the introduction of screening. Furthermore, HIV-positive MSM have an up to 80-fold estimated higher risk than HIV-negative men or women of developing anal cancer.

Head and neck cancers are among the 10 most common cancers reported worldwide. There are several anatomical regions that constitute head and neck cancer, including the oral cavity, pharynx and the larynx. Close to 600,000 cases were reported globally in 2012 with an estimated age-standardised annual incidence of 8 per 100,000 (Ferlay et al., 2015).

In Europe and in the United States head and neck cancer is more common in males with an almost 4 fold difference compared with females.

The incidence of head and neck cancer has been rising in the past number of decades. Within the head and neck region, it has been clear that this dramatic rising trend is mostly attributed to oropharyngeal cancer (OPC). In fact, the fastest growing cancer among all cancers in Scotland has been reported to be OPC (Junor et al., 2010). Among high income countries, the highest incidence for OPC was observed in France for men and in Switzerland for women (de Camargo Cancela et al., 2012). Chaturvedi et al. (2011), reporting on the rise of OPC in the United States, remarked that by 2020, OPC will be more common than cervical cancers and by 2030 half of head and neck cancers will be caused by HPV. Just like head and neck cancer, OPC has a similar male to female distribution, and has been linked to HPV (Kensler et al., 2016). Increasing rates of HPV-transmission and HPV-associated infections have been reported in England over the past 30 years (Health Protection Report, 2007). The rising trend of OPCs has been linked to this rapid increase in people infected with high risk strains of HPV. Patients with HPV-associated head and neck cancers often do not report other major risk factors such as smoking or alcohol use and are younger than HPV negative cases. They are more likely to have a higher number of lifetime sexual and oral sexual partners (d'Souza et al., 2007).

HPV-associated non-cervical cancers now account for over half of the HPV-associated cancer burden in the United States (Chaturvedi et al., 2011). While the transmission and natural history of non-cervical HPV infection is less well understood, the role of HPV in mucosal carcinogenesis is now clearer. In OPCs specifically, HPV appears to have a preference for the lymphoepithelial tissue of the Waldeyer ring, most notably the lingual and

palatine tonsils. HPV-positive tonsillar cancers are believed to arise from deep within the involuted tonsillar crypt epithelium that has a non-keratinised epithelium with much discontinuity of the basal zone, where the virus typically integrates into the host cell genome to replicate. Malignant transformation occurs through the expression of two HPV viral oncogenes, E6 and E7. These oncogenes encode for oncoproteins that bind to and inactivate host cell proteins that normally regulate cell division. HPV-driven cancers outside the tonsils, particularly in the oral cavity, could be related to ectopic tonsillar tissue, which is not common in the oral cavity, and hence the rarity of such cancers.

### **Testing for HPV in Oropharyngeal Cancer**

HPV testing is recommended as the standard of care for all patients diagnosed with oropharyngeal squamous cell carcinoma (Schache et al., 2014). Several molecular methods are available and these may give divergent results and have limitations. A large US study reported 67% of tumours analysed (95% confidence interval, 61.2-73.3) were positive for High Risk HPV E6/7 oncogene expression. HPV type 16 (92%) was predominant with a much lower percentage of HPV 18 cases (3%) (Jordan et al., 2012). Similar data has been presented by others (Kreimer et al., 2005). The prevalence in South Asia was not clear until a meta-analysis was published recently. Case-control studies from this region reveal significant heterogeneity but suggest higher HPV prevalence in oropharyngeal cancer (OR: 14.66; 95%CI: 6.09-35.26) compared to oral cavity cancer and laryngeal cancer; (OR: 4.06; 95%CI: 3.05-5.39 & OR: 3.23; 95%CI: 1.37-7.61) respectively (Shaikh et al., 2015).

### **HPV vaccination: an effective approach in preventing disease**

There is an effective solution to address the cancer-related burden of HPV. Until recently, two HPV vaccines have been licensed for use: a bivalent vaccine which protects against the two high risk HPV types (HPV16/18), and a quadrivalent vaccine protecting against HPV 16/18 and genital warts (HPV6/11). A new nonavalent vaccine protects against nine of the most common virus types (HPV6/11/16/18/31/33/45/52/58). Both HPV2 and HPV4 vaccines are considered highly effective in females against cervical cancer (Lu et al., 2011). HPV vaccine efficacy has also been demonstrated in males; in a study of 4,065 males aged 16-26 years old, the quadrivalent vaccine was effective in preventing genital warts and anal HPV infection (Giuliano et al., 2011; Palefsky et al., 2011).

In this context, it is understood that it may take a couple of decades to show efficiency of prophylactic vaccination against cancer. It is of interest to note that the Costa Rica Vaccine Trial (CVT) found high multisite (cervical, anal, and oral) vaccine efficacy among women not yet infected with HPV, and also suggests that the vaccine may provide protection against HPV16/18 infections at all mucosal sites among certain women who had been infected with these types prior to HPV16/18 vaccination (Beachler et al., 2016). There is therefore significant potential for HPV vaccination to prevent OPCs, given that the HPV types implicated in this disease can be protected against by the HPV vaccine.

The potential for preventative targeting of an aetiological agent that is directly implicated in the development of numerous cancers and also has a negative impact on the sexual health of both genders is compelling, yet to date; few countries have implemented a universal HPV vaccination programme for adolescent boys and girls. Australia was the first country to initiate government-funded universal HPV vaccination for boys in February 2013 (Aus DOH, 2014). The US recommends universal vaccination, with the Vaccines for Children (VFC) Program funding HPV vaccination for children aged 9–18 years who are uninsured or underinsured (CDC, 2016). In 2014, Austria was the first in Europe to commence a publicly funded universal programme (Smith et al., 2014). Within country, HPV vaccination for boys is recommended in Saxony (Germany) and Emilia-Romagna/Sicily (Italy). In Canada, of the thirteen provinces and territories, only Prince Edward Island, Alberta and Nova Scotia include boys in their school-based programme (CIC, 2014; Bonanni et al., 2015; Grant et al., 2015; Colbert, 2015), although the provinces of Manitoba and Quebec may soon follow suit (Manitoba Health, 2015; Gouvernement du Québec; 2016). In New Zealand, the nonavalent vaccine will be available to both males and females from January 2017.

Recently, a number of European countries have issued recommendations in relation to universal HPV vaccination the Czech Republic recommending a catch up programme for men and women not vaccinated in childhood (3 doses between 18 and 26 years) (ECDC, 2016), Lichtenstein recommends two dose vaccination for both males and females (ECDC, 2016), and Switzerland recommends vaccination for boys and men aged 11 – 26 (OFSP, 2015). Vaccination of boys is also now under serious consideration in Ireland, the UK, and Norway.

## **HPV and male vaccination: Making the case**

There is substantial debate around the inclusion of males in HPV vaccination programmes (Stanley, 2012; Shapiro et al., 2016). Those countries with female-only vaccination programmes base this around the assumption that as HPV is a sexually transmitted infection, vaccinated females will no longer be able to pass the virus on to males and so males will benefit from 'herd protection'. There is indeed some emerging evidence that herd protection may work. An analysis of high uptake female-only vaccination programs found a ~30% reduction in the number of boys with genital warts (Drolet et al., 2015). Additionally, a retrospective observational study has demonstrated that a high coverage female only vaccination programme affords protection to heterosexual men, although this was conducted retrospectively in one sexual health clinic in Australia and did not record the vaccination status of the men (Chow et al., 2016). Nevertheless, a female-only vaccination strategy renders a number of male populations vulnerable to HPV infection, as indicated below.

Unvaccinated heterosexual males are not protected if they move outside of the herd (due to migration or travel) and have sex with an unvaccinated partner. Even with a high female uptake of >80%, <20% of girls remain unvaccinated and therefore unprotected. For example, although the UK's vaccination programme reaches about 90% of girls; there are many communities where coverage rates are much lower, in half of London's primary care trust areas, under 80% of girls are vaccinated (PHE, 2013) and uptake has been shown to be much lower in ethnic minorities (Bowyer et al., 2014). In addition, there is a growing concern that the new 'academy' schools in the UK may not accommodate school nurses and vaccination programmes as state schools have in the past (Boyce and Holmes, 2013). Compared to the UK, the global vaccination rates are much lower. A recent systematic review on reported HPV immunisation programmes worldwide until 2014, estimated that in more developed regions, 33.6% (95% CI 25.9–41.7) of females aged 10–20 years received the full course of vaccine, compared with only 2.7% (1.8–3.6) of females in less developed regions (Bruni et al., 2016).

Worryingly, there is increasing evidence to suggest that unvaccinated women demonstrate more risky sexual behaviour; e.g. multiple sexual partners, anal intercourse and smoking (Sadler et al., 2015). These unvaccinated females have the highest attributable risk for HPV-related cancers. Male vaccination would help reduce the risk of HPV infection in this unvaccinated group.



The incremental benefit of extending the vaccine to males is widely believed to be highly dependent on coverage in females. However, a European study assessing the benefit of male vaccination versus a high uptake “girls-only” vaccination program, demonstrated that vaccination of 12 year old boys and girls would be associated with substantial additional clinical benefits in terms of reduced incidence of HPV-related genital warts and carcinomas (Marty et al., 2013).

### **Combating HPV in men: the targeted vaccination approach**

In some countries with a high female uptake, and therefore potential reduction in HPV-related disease in heterosexual men, it has been suggested that the vaccine be extended to ‘high-risk’ men such as MSM who do not profit from female-only vaccination strategies or those men with HIV. This approach attempts to balance protection versus cost, protecting a high risk population while avoiding the cost of a universal vaccination programme (Castle and Maza, 2015). In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) has recently issued a recommendation that MSM up to age 45 years should be offered HPV vaccination via Genito-Urinary Medicine (GUM) and HIV clinics with the possibility of opportunistic vaccination via GPs. A pilot programme is currently being undertaken in England to assess the feasibility of vaccinating MSM. Similarly, British Columbia (Canada) offers HPV vaccination for free to girls and “at-risk” boys (such as boys who are homeless or gay). However, this approach may have limited efficacy in preventing HPV-related disease, as the HPV vaccine is thought to be most effective when given at a younger age (9-15 years), before exposure to HPV through sexual contact and when immunogenicity is at its highest (FDA, 2011), and many MSM are likely to have had multiple sexual partners with increased risk of HPV acquisition before they attend a sexual health clinic (Zou et al., 2014).

### **Cost Effectiveness of universal HPV Vaccination**

Cost-utility analysis is widely used in high-income countries to inform decisions on efficient health care resource allocation. Bogaards et al. (2015) presented a Bayesian evidence synthesis of the incremental benefit of vaccinating boys along with girls in preventing HPV associated cancers in men in the Netherlands. Their estimates suggest that to prevent one additional case of OPC among men, 795 boys (660 to 987) would need to be vaccinated with tumour specific types of HPV vaccines. Graham et al. (2015) demonstrated that compared with no vaccination for the prevention of HPV-OPC, assuming a 99% vaccine efficacy and a 70% vaccine uptake, male vaccination with the quadrivalent vaccine produced 0.05 more



QALYs and saved \$145 Canadian dollars per individual (Graham et al., 2015). A wider socio-economic perspective further supports this assertion, with increased benefit to society characterised through improved productivity, increased earnings and enhanced tax revenue due to vaccine related reductions in mortality and morbidity (Kotsopoulos et al., 2015).

We argue that the most effective, practical, ethical and potentially cost effective solution for citizens in our society is to offer HPV vaccination to both adolescent males and females that might ultimately lead to control of HPV related diseases in men and women alike (The Times, 13th June, 2016). Considering the tragic outcome to a young person affected by head and neck cancer, we emphasise the importance of every public health measure that can be brought to bear to underpin increased cancer prevention. As indicated in this brief review, the evidence base is firmly established. We now need the political will to act upon this evidence.

#### **Conflict of interest:**

GP, ML and SW have no conflicts of interest to declare.

PB is an independent consultant on men's health. He is Campaign Director for HPV Action, a NGO representing and funded by 44 patient and professional groups, and Director of Global Action on Men's Health. In the last two years, he has also provided consultancy services for, or received honoraria from, the European Men's Health Forum, the Men's Health Forum (Great Britain), Sanofi Pasteur MSD, Pfizer, Eli Lilly, the Health Service Executive (Ireland) and Nugensis.

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